potassium by approximately 0.1 mEq/L. That is shown by the light gray bar on the left. Yet, Avalide at the 325 mg dose has an intermediate effect on potassium. It has a small decrease of less than 0.1 mEq/L as shown by the yellow bar in front.

This avoids the hyperkalemia of irbesartan and minimizes the hypokalemia of hydrochlorothiazide. The actions for irbesartan and hydrochlorothiazide offset each other.

[Slide.]

In this original NDA, the safety of Avalide was consistent with that of the current registrational program.

Here, in several clinical studies, the overall rates of adverse events were similar among Avalide, irbesartan monotherapy, hydrochlorothiazide monotherapy, and placebo. Serious adverse events were uncommon, and they occurred with similar frequencies among all treatment groups.

Normally, one might expect a combination therapy to have substantially more adverse effects

than either individual component. However, Avalide has a drug with placebo-like tolerability, irbesartan. Its other component, hydrochlorothiazide, also has excellent tolerability when used at low doses of 12.5 and 25 mg. So, Avalide offers a way to provide increased efficacy without compromising safety.

[Slide.]

Ten years of post-marketing surveillance data also support the safety of Avalide. With over 10 million patient years of exposure to Avalide, and even more on irbesartan, the incidence of reported cases of adverse events has been low. A large group of potential adverse events were reviewed. This list went beyond the adverse events of special interest in Studies 176 and 185.

They included the potential metabolic alterations of hydrochlorothiazide, and they included rare reports of idiosyncratic events that have not been seen in this program, but have been reported in the literature.

These data are presented in the briefing

book on page 42. There were no safety concerns.

In conclusion, the current registrational program, original NDA, and post-marketing surveillance all support the safety of Avalide.

[Slide.]

Studies 176 and 185 were important to show low risks of hypotension and syncope in moderate and severe patients all titrated to the maximum dose of Avalide. This is the key consideration for the evaluation of first-line use. Overall, Studies 176 and 185 show few dose-dependent side effects. The data are consistent with a larger original NDA program that included several long-term studies.

There is no signal of rare, potentially dose-independent side effects from the hydrochlorothiazide component of Avalide in either the NDA or post-marketing surveillance.

Thank you very much.

Dr. Michael Weber of SUNY Downstate Medical Center will now put the benefits of initial treatment with Avalide into perspective with regard to clinical practice.

DR. HARRINGTON: First, before Dr. Weber comes up, let me make sure that the panel doesn't have questions now. I suspect some will.

Go ahead, Lynn.

DR. WARNER STEVENSON: Thank you very much. That was a very clear presentation and quite convincing of the benefit of combining these two agents.

Could you describe a little more for me this population? If I understand the data correctly, they had a mean duration of seven years of hypertension and yet only half of these patients were receiving therapy at the time that you started and went into the placebo run-in period. So someone had diagnosed this, but not treated it for seven years? It's either an interesting physician population or a patient population.

DR. LAPUERTA: Our definition of untreated is not having received treatment within the past month. So, there may be some patients who had received treatment and for some reason discontinued. Unfortunately, we didn't collect

that type of information on the complete medication history. So, we don't know how many were truly naive or just had not received any recent treatment.

DR. WARNER STEVENSON: Could you just tell us what antihypertensive medications they on, just in general, for those people, the 50 percent who had to discontinue a medication, just what was the distribution roughly?

DR. LAPUERTA: Yes. A small proportion were receiving an inhibitor of the renin-angiotensin system. Perhaps that was most common among the types of classes of prior therapy.

Slide 33-11, please.

[Slide.]

There was a mix with 22 percent receiving an ACE, 12 receiving an angiotensin receptor blocker as prior treatment, and then beta blockers and calcium channel blockers.

DR. LINCOFF: I have a question and a couple of points. First of all, you had mentioned for the second study, the 185, the secondary

endpoint was for a portion of patients who reached 140/90, the same as the primary endpoint for the previous study.

I would like to see that, because as a previous speaker had mentioned, I, too, am sort of inclined to consider the moderate hypertensive indication, as well, and it would be nice to see that sort of data.

Do you have that?

DR. LAPUERTA: Yes, Slide 25-104, please.

[Slide.]

These are results at every time point. The primary endpoint was at Week 8 in Study 185. So, here, irbesartan could achieve blood pressure control to less than 140/90 in 40 percent of patients.

The differences between irbesartan and Avalide were statistically significant with more control on Avalide.

DR. TEMPLE: When you presented Study 176, on Slide 39, you had what we keep asking about, which is a display of the relationship between

achieving goal and the starting blood pressure. Do you also have that for 185? I am sure you do.

DR. LAPUERTA: Yes, we do. We have it for both 176 and 185, and the same relationship was seen in Study 185. The further you are away from goal, the more likely you are to need more than one drug to achieve it.

We have this for 185 for control to 140/90. That is what I would like to share with you, and we have it next to the results for Study 176, baseline systolic blood pressure predicting your probability of achieving control to 140/90.

Slide 51-48, please. No, this is not the slide I wanted. I want one comparing 185 and 176, the proportion of people achieving a blood pressure of less than 140/90.

No, the relationship between systolic blood pressure and the probability of achieving a blood pressure less than 140/90, Slide 51-101. Thank you very much.

[Slide.]

I thought it would be good to present the

two studies next to each other to compare and contrast where you achieve blood pressure control and where monotherapy starts to control the majority of patients.

In Study 185, you can see the baseline systolic blood pressures of less than 160, so baseline systolic blood pressures in the mild range. One starts achieving blood pressure control to 140/90 with monotherapy in the majority of subjects.

So, one could say potentially that this is consistent with JNC guidelines, that patients with moderate hypertension, the majority require two drugs, and in this study, patients with milder systolic blood pressures, maybe their diastolics are high, but milder systolic blood pressures could be controlled with irbesartan.

DR. TEMPLE: It would also be of interest to see other goals. I mean presumably if the moderate people were diabetic, you might want to get to a lower blood pressure, something like that.

I am asking about this because one of our

thoughts was that we could display a lot of this stuff in labeling to give people an opportunity to make intelligent judgments. But one question we have is can people cope with this. I am not sure I know the answer to that. It is more informative, but we don't want to overwhelm people either.

DR. LAPUERTA: Slide 51-24, please.

DR. WARNER STEVENSON: Leave that slide.

DR. TEMPLE: I should say again you don't in any of these show the diuretic. That presumably will come out as a lower line, because in your data, the diuretic alone in 185 had a somewhat smaller effect.

DR. LAPUERTA: While this slide is up, I may as well speak to it.

DR. WARNER STEVENSON: Do you happen to have that at the same time point just out of curiosity, which would have to be Week 5, I guess, for the 18t? I am just curious, because it's a longer time interval for the second one.

DR. LAPUERTA: No, we don't have this for the same time point. The evaluations were at I

believe Weeks 6 and 8 for the moderate study and Weeks 5 and 7 for the severe study. So, we don't have exactly the same time points.

DR. LINCOFF: Also, before you leave this slide, because I had a comment on the original 39. It is striking on the left side that although, obviously, the lower the baseline blood pressure, the larger proportion reach goal even with monotherapy. But also the difference between the therapies is greatest at the lower levels, so that if you are looking at these, not as a combination versus a single, but just as two different competitive agents, it is striking that actually the most incremental difference is actually in the lower blood pressure ranges.

Again, I think this gives some weight to the idea that in the moderate hypertension range--now granted the right side doesn't quite show that, but then it doesn't go as high, et cetera. But I am struck by the idea that you seem to have more advantage even in the lower ranges where there is a bigger increment.

DR. HARRINGTON: Although the only thing here, Mike, is that you are not seeing the confidence intervals and that there are far fewer patients at the lower level than there are at the higher level.

DR. LINCOFF: Yes, I don't know what the samples are at that point, but it is a smoothly defining curve. I mean it's not a line bouncing around.

DR. LAPUERTA: To Dr. Temple's question, I can show the relationship between baseline blood pressure and the probability of achieving a target of 130/80.

Slide 51-24.

[Slide.]

This is in Study 176, not Study 185, but it underscores how difficult it is to achieve a blood pressure of 130/80 with monotherapy. It is difficult even with two drugs when the patient has severe hypertension.

I do have this for Study 185, which is more direct to your question.

Slide 51-87.

[Slide.]

Here again it is difficult to achieve systolic blood pressures less than 130. So, even in moderate hypertension, patients with a target of 130/80 will need at least two drugs to achieve blood pressure control.

DR. PAGANINI: One other quick group, again going back to Slide 37 and 38 as your subgroup analysis, do you have that for 185 at all? Do you have any other data looking at anyone with CKD Stage 2 or greater and their response as a subgroup analysis?

DR. LAPUERTA: I will be glad to review that. I wonder if I could just show the confidence intervals since someone asked about confidence intervals before, and then we will review that.

That is Slide 51-32, please.

[Slide.]

We have not presented the confidence intervals before because they make the chart more complicated, but since this was requested, I

thought it would be helpful to review them briefly.

Now, your question is about subgroup efficacy analysis in Study 185 and patients with renal disease, correct?

DR. LINCOFF: Correct.

DR. LAPUERTA: An important subgroup in Study 185 was the African-American population.

Slide 25-59, please.

[Slide.]

Here, we see that irbesartan monotherapy lowers blood pressure less in blacks than in non-blacks. However, the response to Avalide approaches that of whites.

I believe we also have results for hydrochlorothiazide in the black population in Study 185, and I think that would be informative, as well, to bring up.

Slide 25-136, please.

[Slide.]

So, blacks respond well to a diuretic. Now, the numbers here are small, because there weren't that many African-American subjects in

Study 185. But Avalide was still beneficial compared to a diuretic in this study, at least that is the point estimate.

DR. WARNER STEVENSON: I think one point, at least one other study, patients with creatinine over 1.5 were excluded.

DR. TEMPLE: That tends to show that blacks respond very poorly to the diuretic.

DR. LAPUERTA: The number of people is only 12 subjects, so that is a small sample size.

DR. TEMPLE: But it is somewhat surprising. I think most people would have expected a bigger response to diuretics and a smaller response to the ARB.

DR. LAPUERTA: Yes.

DR. HARRINGTON: That brings me to a question or maybe a theme that Emil brought up earlier, and it really was borne out for me on one of Bill Weintraub's slides where he showed the demographics of mild, moderate, and severe hypertension in his population.

The demographics of his moderate and

severe population are much different than what was studied here. There were more blacks in Bill's population, a lot more diabetics, I suspect more chronic kidney disease, et cetera. So help me understand how to make decisions regarding the generalizability when these patients aren't being studied.

Now, we have a little bit of an advantage here with Avalide because you have 10-plus years of market experience. But if part of our charge today is to think about the broader issue of combination therapy, and some of the questions get to what should be the requirement for considering that, for me, the generalizability and understanding the population in which it is ultimately going to be used is a critical one.

DR. LAPUERTA: Well, we do have data on the response to Avalide in African-Americans from other studies, that show in general, as the label says, that their response is similar to that of whites.

In terms of why we had so few

African-Americans in the study, we actually discussed this with the Food and Drug Administration, and there was concern that one could bias the study against irbesartan monotherapy by selectively over-enrolling African-Americans. So, to provide an unbiased study from that perspective, we recruited patients from Europe, as well, and we kept the percentage of African-Americans to only 14 percent.

DR. TEMPLE: This distinction in response has been noticed since the beta blockers. There is an important VA study from a million years ago that showed, with what, I guess natalol--that natalol monotherapy had very little effect in the black population. But, when you combined natalol and the diuretic, it looked the same, more or less the same in whites and blacks. And there have been subsequent studies with ACE inhibitors and ARBs, most of which show that, and this shows a pretty nice response for the combination. It actually almost looks super additive. I don't know whether you should believe that given the small numbers.

So, there is a fair experience with that, but it is true, you can make your combination look better by having a lot of blacks who don't respond very much to the ARB. So, we would have worried about that to a degree.

DR. HARRINGTON: Although you could make the other argument that at least looking at the Weintraub data, that that is the population.

DR. TEMPLE: Right. I think most people would say that when you take an angiotensin receptor kind of drug, a renin-angiotensin kind of drug, you probably get a lot when you add a diuretic to it. I mean that is sort of everybody's bias in the black population, but what to study in addition. They did have a separate study of Avalide in the black population.

DR. LAPUERTA: Should I return to Dr. Paganini's question? I haven't finished answering it, if that is all right, your question about subgroups?

DR. PAGANINI: Yes. The only other subgroup would be the CKD, understanding that there

is a 1.5 creatinine, you still have Stage 2/3 that are available there.

DR. LAPUERTA: Yes, we did have some patients, not very many, with these levels of kidney function. In general, we examined as to whether that was a predictor of response to therapy, and it was not a predictor of response to therapy.

DR. PAGANINI: And finally, the subgroup of diabetics in the 185.

DR. LAPUERTA: One moment. Slide 25-207, please.

[Slide.]

This is stage of renal function. This is Study 176, not Study 185. It shows a general consistency in terms of blood pressure lowering of Avalide in the range of 30 to 37 mm of mercury, and diastolic lowering in the range of 24 to 26 mm of mercury in subjects with different levels of kidney disease.

Because of the small sample size for Stage 3 kidney disease, it is difficult to say if that is

really a trend for more efficacy with more advanced kidney disease.

You also asked about diabetes. I have diabetes data for Study 185 on Slide 25-132.

[Slide.]

So, these are the results. Avalide lowered blood pressure more than the monotherapies in diabetic patients.

DR. HSU: As a statistician, I was a little curious why the primary endpoint changed from 176 to 185. Any particular reason?

DR. LINCOFF: One of the reasons we had a different primary endpoint in Study 185 is because we realized that all blood pressure parameters were important, and it was difficult to make a decision.

I mean, we also knew that blood pressure lowering of systolic and diastolic blood pressure are highly correlated so, since we had difficulty making a decision, we stuck to diastolic. It was consistent with the Hyzaar program that was registrational and that had preceded us for Study 176, and systolic for Study 185.

DR. LINCOFF: Can you help me understand a bit more about the details of your adverse-event collection. I am concerned when you go into a study with the idea that a key part of this study is risk/benefit, and you want to know the safety issues, and then you don't collect them as endpoints but, instead, you collect them as AEs--because the systematic collection with AEs is generally not as systematic as it would be if you had at fixed time points or at least fixed questioning for endpoints that were safety endpoints. These AEs of interest, for example, had they been endpoints, might have been collected more systematically.

So, can you reassure us that these AE reporting were as systematic?

DR. LAPUERTA: Well, the AE reporting was discussed with the investigators as one of the primary reasons for doing the study. You know, was 150/12.5 too high a starting dose for patients with severe hypertension, and was titration at just one week in everybody to maximum dose, too much for

patients.

So, it was understood generally by the clinicians as the real reason for doing the study. Everyone expected Avalide to lower blood pressure more than its individual components. So, that was the conduct of the study.

In terms of analyses, we have done additional analyses of blood pressure to look for any potential signal of hypotension that may not have been reflected in the adverse events.

One analysis that I would like to share with you is analysis of orthostatic changes. I mean that is a question. Maybe even if physicians haven't reported symptoms in their patients, when patients stand, the systolic blood pressure might drop 20 mm, the diastolic blood pressure might drop 10, and that could be a sign of a risk for an adverse event.

Slide 35-175, please.

[Slide.]

So, at baseline, and this is on placebo prior to initiation of therapy, approximately 3

percent of subjects in each treatment group had orthostatic changes. Over time, that actually gradually reduced on Avalide. So, there was no increase in orthostatic changes with Avalide compared to irbesartan monotherapy.

So, we feel to some extent that examining the blood pressure changes in detail can provide some reassurance about potential for hypotensive events that maybe weren't sensitively recorded by all physicians.

DR. PAGANINI: Sorry to keep you up there. Slide 48, could you expand a bit on your lack of efficacy in the two groups that you had? Could you give us some sort of an analysis of what that meant?

DR. LAPUERTA: Slide 48, please.

DR. PAGANINI: The second line, 3.2 and 5.2 percent of subjects, lack of efficacy. Does that mean in trial, they didn't move at all in blood pressure?

DR. LAPUERTA: I don't have the exact blood pressure changes of those subjects, but, in

general, we did see these discontinuations because physicians were concerned that the blood pressures were still severe after 3 or 5 weeks of treatment, and so the patients were discontinued to get more aggressive therapy. Some of the physicians may have been concerned that the patient was at risk and not getting enough medication.

DR. PAGANINI: Was this during a placebo run-in? Was this during the first week or two weeks before you went to max therapy? Was this after you received max therapy? Were some of the physicians a little bit concerned about not receiving something, and pulled them off early from the trial? Any type of description?

DR. LAPUERTA: This was generally between Week 3 and Week 7, that is correct. There were a few discontinuations between Weeks 1 and 3. Physicians wanted to give the therapy time to work.

DR. HARRINGTON: Do you have the concomitant medications that these patients were on in the two studies, I mean statins, diabetes drugs, et cetera, just to give some perspective as to how

they were treated?

DR. LAPUERTA: Yeah, we do have these data. I don't recall if we have a slide to show you. I can come up with some of that data during the break, because it's in our final study report.

One thing I can say is that there were very few cardiovascular comorbidities compared to, say, Dr. Weintraub's population, and one of the reasons may be that we had so many patients not on any prior therapy. Patients that had a history of a heart attack, ideally, they would have been on at least two blood pressure lowering medications, a beta blocker and an ACE inhibitor.

DR. HARRINGTON: Although you also excluded patients who had had a recent coronary event, I think it was within 6 months or something.

DR. LAPUERTA: So, I was struck in general that the incidence of cardiovascular complications in this population was low, and it was because of the entry criteria, that we wanted a naive population as much as possible.

DR. HARRINGTON: Before you go, I have a

question for Norm. Norm, where did the 10 percent come from on the Hyzaar, because we are going to talk about that. This essentially failed at what it set out to do, which is to show--because irbesartans perform so well, but where did the 10 percent come out? Help us understand that.

DR. STOCKBRIDGE: I am sure the 10 percent cannot be justified. It was--

DR. HARRINGTON: Under previous leadership?

DR. STOCKBRIDGE: It was definitely under some previous leadership, but I think the basic philosophy was you didn't want--at the time was you didn't want to get people on two drugs unless you were pretty sure you were going to need them and pretty sure, in this case, translated to 10 percent.

DR. TEMPLE: It was when do you have an exception to the philosophy of step care, where you actually give equal two drugs, one of which they may not necessarily need. So a very high standard was set, because we were evolving from quite a

different philosophy.

Maybe part of it is that the drugs people are looking at are more benign than they used to be, so the idea of giving two, you know, giving an ARB with something and a low-dose diuretic isn't so horrifying because they don't do very much that is bad, as we just saw.

It was intended as a very tough standard to overcome a basic principle, which is don't use two if one will do.

DR. HARRINGTON: Thank you very much. It was, I agree with the other panelists, it was a very clear presentation. Maybe we will hear from Dr. Weber, some questions, and then we will take a break and then have a more detailed discussion.

DR. LAPUERTA: Okay. I do have one question, though, because, Dr. Harrington, you asked a couple of times about African-Americans, would it be okay before Dr. Weber comes up to show you some more data?

DR. HARRINGTON: Absolutely.

DR. LAPUERTA: Because we do have a

post-marketing study called INCLUSIVE, that had larger numbers of African-Americans, so we do have more robust information there.

This study was called INCLUSIVE, because it was meant to include patients populations like African-Americans and diabetics that maybe had not been as extensively studied. 25-182.

[Slide.]

These are populations that are difficult to control. Here, we see on Avalide the systolic blood pressure lowering of 21 in African-Americans and then 22 mm in whites. The diastolic lowering is comparable. So, now we have numbers that are a little bit larger, 157 here, and we show comparable efficacy to the white population.

DR. HARRINGTON: So, why don't we hear from Dr. Weber and maybe ask questions. Maybe we will take a break and then come back and hear your summary.

Benefit/Risk Profile

DR. WEBER: I am going to talk about benefit and risk, and take a fairly simple tack in

how I am going to think about these issues.

[Slide.]

First of all, I will talk about the overall rationale of how we have thought about talking about benefit and risk, and then I am going to talk a little bit about risks themselves, what they might be, and then finally, the benefits.

I will talk about avoiding severe blood pressure elevations, which is a sense is the primary focus of the sponsor's presentation, and the importance of treating severe hypertension. But I also want to talk about possible long-term blood pressure advantages, which I think may be a very important outcome from starting treatment with a combination, and based on that, also the possibility that effective long-term blood pressure reduction translates also into better cardiovascular protection.

[Slide.]

This is the basic rationale for what I wanted to argue in considering why we might want to consider a combination of an ARB and a thiazide to

start off therapy.

The obvious comparisons you would want to make is how does the combination stack up against an ARB alone and how does it stack up against hydrochlorothiazide or a diuretic alone.

The argument that we want to make is that comparing the combination with irbesartan or the ARB alone, safety is pretty much equal certainly during the first few critical weeks. But. clearly, there is greater efficacy.

If we consider the other possibility, the combination compared with hydrochlorothiazide alone, we would make the argument that there is the potential for greater safety, as well as greater efficacy.

[Slide.]

Let me start by showing a much talked about and widely quoted study published two or three years ago by Law and colleagues in the British Medical Journal.

This is a meta-analysis of 50 studies culled from the literature in which low-dose

combinations were studied and where it was possible to look at the individual ingredients of each of the combinations, as well as the combinations themselves.

If we look on the left, one combination component typically is low-dose diuretic. The second of the combination component most typically is an ACE inhibitor, an angiotensin receptor blocker, a beta blocker, rarely a calcium channel blocker.

The point that Law makes is that at least in terms of low doses, you get pretty close to full additivity when you give people a combination. Higher doses may be slightly different, but certainly low-dose combination starts that way.

[Slide.]

The conclusion that Law and colleagues drew and published is that certainly as far as safety is concerned, that the minimal metabolic effects of low-dose diuretics, most commonly 12.5 of hydrochlorothiazide, did not compromise safety, and clearly, the incremental blood pressure

benefits you get from using a combination would be projected to have cardiovascular protection.

[Slide.]

The single biggest risk that we would worry about is the possibility that, if we started treatment with a combination of two drugs, there might be an excessive or precipitous fall in blood pressure. I don't think any other risks would match up to that in terms of our concern.

We have already had the opportunity this morning of looking at data from two very relevant studies, Study 176, the one done in severe hypertension, and as Dr. Lapuerta has already shown us, there was an incidence of 0.6 percent of hypotension on the fixed combination.

However, this did not occur at all when the drug was started, but only sometime into the study after patients had been force titrated to a higher dose even though their response to the initial low-dose combination had been very effective. In clinical practice, these people certainly would not have been pushed up to a higher

combination dose.

Likewise, in the moderate study, 0.9 percent incidence of hypotension, again, two of three patients there had been pushed up to a higher dose even though they had had good early response to the lower combination dose. Again, no one actually had hypotension right at the beginning of the study.

That is always a little difficult talking about this, because we only know blood pressures when they are measured. We don't know that people might not have been hypotensive at times away from the doctor's office. Nevertheless, driven by symptoms and reports of patients, these seemed to be pretty accurate representations of what took place.

So, I think we can be reasonably comfortable that major threatening falls in blood pressure are unlikely events.

[Slide.]

Why is it possible that, if we do what many of the guidelines say to do, JNC 7, for

example, and start most patients with a thiazide for the treatment of the hypertension, why is that possibly a greater risk than starting treatment with a combination?

First of all, if you use a thiazide in the sorts of doses that are likely to reduce blood pressure, and 6.25 and 12.5 mg of hydrochlorothiazide are not likely to reduce blood pressure in many people, if we are talking about using at least 25 mg, then, it is almost certain that we will produce metabolic changes. Pablo already showed us his analysis of what thiazide monotherapy does to potassium. It is something we are all very familiar with.

[Slide.]

The second issue is if we, for example, said let's start with the diuretic and then later on add the ARB, there I believe we have a greater possibility of causing hypotension.

In fact, this is already acknowledged in the Avapro package insert--which, by the way, is not unique to Avapro; it is virtually the same

insert for all ARBs, ACE inhibitors, and even the new renin inhibitor--and that is, if you start a patient on a diuretic, cause volume depletion, and stimulate the renin-angiotensin system, there is a risk if you now add in the block of the renin-angiotensin system of getting a precipitous fall in blood pressure. In fact, many package inserts advise stopping the diuretic for a couple of days before adding an ARB or an ACE inhibitor, which is something frankly that I doubt if any physicians actually do.

So, my argument would be that hypotension is more likely in that setting than we have seen with the use of a combination as initial therapy.

[Slide.]

What are the benefits of avoiding severe blood pressure elevations? We have already seen those data from Dr. Lapuerta in the 176 study, and we have seen that the combination is effective at protecting people from very severe hypertension.

I am also interested in pursuing the longer term effects and looking at decrements of

blood pressure that might be important over sustained treatment periods.

[Slide.]

This is just to remind you of the same data that you have already seen. This is from the 176 study. And if you look at the possibility of people having severe hypertension during that trial--in other words, systolic of 180 or higher, diastolic 110 or higher--you can see that compared with Avalide, people who were just on irbesartan alone are much more likely to have severe hypertension.

Likewise, if we look at so-called moderate hypertension, at people between 160 and 179, or 100 and 110, again, clearly less likely to occur if patients are on the combination and, if you pool it all together, JNC 7, Stage 2, again you see the protective effects of starting with the combination.

[Slide.]

Tom Giles showed the original VA Cooperative Studies. It is fascinating actually

that the first was published exactly 40 years ago, which many of us regard as the birth of hypertension as a discipline.

You can see--if you look at the extreme right from the two VA studies and also a study from the NHLBI, you can see the excess risk of events--in other words, hypertensive emergencies--in patients who have severe hypertension who are not treated, and you see 27 percent, 11 percent, 14 percent.

In other words, the risk of hypertensive emergencies is real in people with high blood pressure. It just makes the important point that there is a virtue in treating severe hypertension for that reason alone.

[Slide.]

I must confess, somewhat along the lines of Dr. Temple's early questions, a big interest, though, in the further benefits over the longer haul in patients who are not necessarily as severe.

We see that in Study 176, compared with irbesartan, the combination had a 10/5 mm of

mercury advantage by the end of the study.

In the moderate trial, compared with irbesartan, the combination had a 5/3 advantage, and compared with the diuretic, 11/7.

I would want to make the argument that these differences are likely to be sustained. We know from clinical trials that blood pressure differences between treatment arms persists long term despite the best efforts of people running the trials and the investigators conducting the trials, to remove the differences between the treatment arms.

Many of the hypertension studies, as we well know, in the sense of being compromised because of the difficulty of interpreting outcomes in treatment arms where blood pressures have been different despite all efforts to avoid that.

Of course, we have epidemiologic evidence. We have already seen some from Dr. Giles and Dr. Weintraub indicating that again small differences in blood pressures are important.

[Slide.]

I shan't waste time talking about this important work from Lewington and clinical trial as collaboration. Tom showed these data before, making the point that a 20 mm of mercury difference in systolic pressure is associated with a doubling in risk of major events.

The same statisticians made the point that you could reduce that down to a 2 mm of mercury difference translating into approximately a 10 percent relative effect on the likelihood of major outcomes.

[Slide.]

We already know, as I pointed out, from a number of trials that inadequate blood pressure responses were never fully corrected.

This was typical for the ASCOT study, for the VALUE trial with which I was closely connected, and the ALLHAT study. I think you could also add, if you like, the HOPE trial to that, because HOPE was also greatly influenced by apparently small, but nevertheless meaningful, blood pressure differences.

Right now there is another study going on called ACCOMPLISH, which is interesting because it is a comparison right from the beginning of two combinations used as initial therapy.

Interestingly, in that study, not only have there been remarkably few adverse events reported, but they have achieved clearly the highest control rate ever in a trial of high-risk hypertensive patients. By 6 months, 73 percent of patients were fully controlled.

Those data--incidentally, I have been allowed to mention them--they will be officially presented in a few weeks at the American Society of Hypertension.

[Slide.]

Why is it that if you get off on the wrong foot and don't get blood pressure down as decisively as possible at the beginning, that you tend not to catch up?

There is a lot of literature about this. Since I didn't want to spend a lot of time going into an area that I think, for most of us in the

room who see patients, is fairly obvious, we know that having got off to the start of treatment of hypertension, things don't always pan out as well as we would like.

From a patient point of view, they often find it costly and inconvenient to keep their appointments. Some health plans, for example, encourage patients to refill their prescriptions, but don't make it that easy to come back to see the doctors.

Many prescriptions are renewed by people who did not stop the treatment of the hypertension. All sorts of reasons come up for why once treatment is started, it is never--or I shouldn't say never--but often not subsequently optimized.

It is not just issues related to patients. It is also issues related to physicians. We know that physicians tend to be very cautious, maybe excessively cautious, in avoiding upgrading or intensifying treatment.

We are very much aware of the landmark study done by Dan Berlowitz, who is here this

morning, using the VA as a model, showing that even when patients present with severe hypertension, more often that not physicians will note the severity of the hypertension, even express concern over the severity of the hypertension, but they still, for whatever reason, do not pull the trigger.

[Slide.]

This is ALLHAT. I think all of us have seen this slide many times showing, despite the intent to have equal blood pressure effects in two different treatment arms, one an ACE inhibitor, one a diuretic, the diuretic had the better of things early on, and despite many, many requests of investigators to improve the quality of care, they never completely close the gap. At the end of the study, there is still a 2 mm of mercury difference. Earlier in the study the difference is even greater.

[Slide.]

That certainly had an effect. In ALLHAT, for example, there was a 15 percent difference in

stroke incidence, really a dramatic difference between the two treatments that was explicable totally on blood pressure differences.

In the Syst-Eur trial, which started out as a placebo-controlled study comparing active therapy with placebo, later on when patients were allowed in the placebo arm, and in fact, encouraged to be put on full therapy for a longer term post-study follow-up, they never closed the gap and, in fact, there still remained a big advantage to people who had started earlier. The latter group never caught up for blood pressure or events.

SCOPE is another example of that, and even in the ASCOT trial that is discussed so much, early blood pressure differences were never compensated, and, in the view of the investigators in the subsequent analysis, about 40 to 50 percent of the difference in treatment outcomes between the treatment arms could be explained by the failure to equalize the blood pressure.

[Slide.]

Here is VALUE. Again, a study done by

experienced investigators, comparing an ARB and a calcium channel blocker. You can see within the first couple of months, a 4.0, 4.5 mm of mercury advantage to the calcium channel blocker.

Investigators had options to use just about any drug they wanted to use to get blood pressure under control, and they were exhorted to do so again and again and again.

Eventually, the gap was narrowed to 2 mm of mercury, but never completely was the difference bridged. That also had an effect on outcomes.

[Slide.]

In fact, if you look at the first few months of the study, from zero to 3 months, where the difference was almost 4 mm of mercury, you can see that stroke incidence strongly favored amlodipine, the drug with that 3 to 4 mm of mercury advantage.

Over time, that difference narrowed as the blood pressure difference narrowed, but you can really see why getting blood pressure under control fairly promptly is beneficial. If fact, it is not

an analysis that I would make a great deal of fuss over, but in VALUE, blood pressure at 1 month was predictive of events during the subsequent 5 years. Again, a strong incentive to get blood pressure under control rapidly.

[Slide.]

So, in summary--

[Slide.]

-- what I wanted to say, first of all, about risk is that Avalide has demonstrated its safety profile very strongly. We have seen the data this morning from Studies 176 and 185. We have got the data from the original NDA and also data from post-marketing surveillance, as Dr. Lapuerta has shown.

The meta-analysis I showed from Law and colleagues had shown that low-dose combinations did not compromise safety, and also the fact that as far as risk is concerned, that initial Avalide safety may be better than starting off with a diuretic alone.

We talked about how the combination is

likely to avoid some of the metabolic effects seen with a diuretic and also the danger of sudden falls in blood pressure if we start with a diuretic and add other things later.

[Slide.]

The benefit? In my view, the 10/5 mm of mercury, even if it is compensated for later, I would argue will never be completely eliminated. Likewise, in the moderate study, that 5/3 versus irbesartan, 11/7 versus diuretic, again, adding other drugs later may help to close the gap, but I would argue probably that gap would remain long term.

Even if it was only 2 to 3 mm of mercury, some members of this committee and certainly the representatives of the Agency will remember just two or three years ago, at one of the meetings of the Cardio-Renal Advisory Panel, there was a discussion comparing two ARBs, one wanting to claim superiority over the other because of a 2 to 3 mm of mercury difference. In fact, that claim was granted by the committee and became part of the

labeling for that drug because it was felt that a 2 to 3 mm of mercury difference was clinically meaningful.

As I pointed out, we believe that early advantages in blood pressure reduction persists and potentially are associated with improved outcomes.

[Slide.]

This is my last slide and my final conclusion. Very simply, initial use of Avalide fixed combination as compared with starting with a monotherapy provides greater efficacy without compromising safety.

It is obviously appropriate for patients with severe hypertension, and that is clearly the stance that the sponsor has taken in its argument this morning.

I would argue that we should be thinking more broadly. I put that the data would suggest and support guidelines recommendations that patients who are 20/10 mm of mercury away from their goal would also be candidates.

I am not suggesting necessarily that

numbers be put into labeling. I am not sure that 20/10 is the right number but, nevertheless, it does indicate that for those patients where we believe that one drug is unlikely to allow a patient to reach goal, where we also have a belief that it is important to be relatively prompt in getting blood pressure under control, and certainly, as Dr. Temple raised, for patients at increased cardiovascular risk, people with diabetes, chronic kidney disease, and coronary heart disease, again, an incentive to get the blood pressure down decisively right from the very beginning.

Thank you very much.

DR. HARRINGTON: Are there questions from the group? Go ahead, Emil.

DR. PAGANINI: I stand between everybody and a break, so I am going to try to keep it as quickly as possible.

We have seen 5-week and 8-week endpoint blood pressures. We are also under the impression, and probably rightfully so, that blood pressure is

a surrogate for long-term outcome problems.

Do we have any data post-market, now 10 years with this drug, of long-term complications with this drug over time, and do we have any direct outcome data with this drug, observational as it is, with cardiovascular, stroke, or any other progression of disease data that we might have specific to this combination drug rather than using short-term effects for long-term outcomes? Do we have any long-term outcome effects?

DR. WEBER: Well, the one important long-term study with major outcomes, of course, would be the one of great interest to you, the IDNT trial, the irbesartan diabetic nephropathy trial, that was done in patients who had diabetes and nephropathy.

They did not start with Avalide. But almost all patients, as you might imagine, finished up getting a combination of irbesartan and hydrochlorothiazide, in many cases other drugs as well, to get the blood pressure under control.

There, you recall, first of all, not only

was there a clear advantage to the patients getting that particular treatment and preventing the major endpoint, but a subsequent paper done by Mark Pohl on behalf of the investigators in that study showed that the degree to which blood pressure was reduced even within the irbesartan/hydrochlorothiazide treated subgroup was predictive of benefit certainly as far as renal protection was concerned.

I think that is pretty comforting information.

DR. WACLAWSKI: Maybe not for this moment, but we also have done an analysis of a managed care database, the PharMetrics database, looking at a population of patients that have been treated with Avalide versus irbesartan versus hydrochlorothiazide to complement that post-marketing experience that Dr. Lapuerta talked about.

So, perhaps after the break we could come to that. I should also note that is a relatively new analysis, so it has not been yet submitted to FDA. But, with their permission, we could share

that with the committee, because I think it provides some reassuring safety data with respect to a comparison in that setting of Avalide versus the two components.

DR. WARNER STEVENSON: I wonder if I could ask our experts in hypertension in general about the elderly population, which is not very highly represented here. It seems that our concern over hypotension would be particularly heightened in the elderly in whom falls are such a major cause of morbidity.

In general, in your hypertension experience, what is the proportion of intolerance of medications due to hypotension in the elderly population, particularly not just over 65, but those over 70, 75?

DR. WACLAWSKI: Dr. Franklin is here. Dr. Franklin has studied and written about elderly and hypertension in elderly, so perhaps Dr. Franklin would be best to give the initial response there.

DR. FRANKLIN: In answer to your question, it is very reassuring that the data that has

already been shown, comparing side effects in elderly individuals over the age of 65 versus younger people, under the age of 65, that there were no significant differences in side effects overall, and certainly not in hypotension and syncope.

Now, in terms of the elderly, as both the NHANES and the Framingham Heart Studies have shown, there is actually more resistance to good blood pressure control with increasing age.

In terms of drug therapy, even though it has been said that we have to be exceedingly careful in using drugs in our elderly population, the original SHEP study of isolated systolic hypertension, published back in '91, showed very good tolerability, very little excess hypotension in the elderly population.

I think there is one caveat that we have to keep in mind in terms of a message to physicians, and that is, perhaps during the initial establishment of hypertension and during the titration period, that one should use standing

blood pressures, as well as sitting blood pressures, in order to rule out significant orthostatic hypotension.

DR. HARRINGTON: Other questions? Go ahead, Bob.

DR. TEMPLE: One observation. Two of the most impressive study results ever are SHEP and Syst-Eur, which were done entirely in people, I think, over 70, and at least one of them used a calcium channel blocker. So, if you are going to worry about orthostatic problems, you would probably worry more there than the renin-angiotensin drugs. It still worked out pretty well.

DR. HARRINGTON: It's 10:40. Why don't we take about a 15-minute break. We will start, so that your presentation can frame the discussion. We will about an hour's worth of discussion and then we will break for lunch.

[Break.]

DR. HARRINGTON: We will start with your concluding remarks and then we will have some

discussion.

Conclusions

DR. WACLAWSKI: Thank you, Dr. Harrington.

The FDA is considering new criteria for approving fixed-dose combination products for hypertension. These new criteria are based on a characterization of the tolerability and efficacy of the combination and labeling that describes the efficacy of the combination across a range of baseline blood pressures.

[Slide.]

The Avalide program has played a role in developing these new criteria. Although the Avalide program originally intended to follow the same path as Hyzaar, the Avalide study assessed the safety and tolerability of Avalide in a less heavily pretreated patient population, which may have explained why more monotherapy patients achieved the diastolic goal with irbesartan.

Nevertheless, the study was positive. It established a reassuring safety and tolerability profile of initial use of Avalide with a

substantial efficacy advantage.

The data can be used to describe the relationship between baseline blood pressure and the chances of reaching goal blood pressure, giving physicians information needed to gain an appreciation of what to expect from Avalide across a range of baseline blood pressures.

These data support the approval of Avalide for initial use in severe hypertension. Avalide, compared to irbesartan monotherapy, lowers blood pressure further, more rapidly, in a higher proportion of patients, and the better efficacy came without a cost in terms of safety and tolerability.

Specifically, in the Avalide trials, hypotension was infrequent and not severe. We encountered no syncope, and the risk of the most frequent dose-dependent side effect of hydrochlorothiazide, hypokalemia, is lessened when hydrochlorothiazide is combined with irbesartan.

The dose-independent side effects of irbesartan and hydrochlorothiazide are rare. The

risks of these side effects with either component are substantially outweighed by the efficacy provided.

These conclusions are based on the results of the new Avalide studies, data from the original NDA, post-marketing data, and a meta-analysis published by Law and colleagues.

Based on our data, we propose that Avalide be approved for first-line therapy in patients with severe hypertension. To implement this proposal, the current Avalide labeling would need to be revised.

[Slide.]

First, to add an indication for initial use in hypertension. The specific wording of this indication is one of the issues for discussion today. We are open to that discussion at this point in the regulatory process and look forward to working with the FDA on arriving at the appropriate indication that describes the patient population.

Second, we would remove the statement in the Dosage and Administration Section that requires

titration of one of the components before using Avalide as an initial treatment in that population where it was indicated as initial therapy.

Finally, the labeling should provide guidance to physicians. A major element of that guidance is a description of what to expect in terms of blood pressure lowering from using Avalide or irbesartan alone.

These figures show that relationship between baseline blood pressures and the chances of reaching a goal blood pressure, and they are proposed as part of that guidance to physicians that could be part of labeling.

[Slide.]

If we are successful, physicians will be able to use Avalide appropriately as initial therapy, resulting in a reduced exposure to severe hypertension with the potential for fewer hypertensive emergencies and lower blood pressures potentially leading to fewer cardiovascular events.

We look forward to the committee's perspective on our proposal to revise the Avalide

labeling.

Thank you.

I will now moderate the question and answer portion of our presentation.

DR. HARRINGTON: I am just trying to recall, Dr. Waclawski, was there some additional data you were pulling out for Emil?

DR. WACLAWSKI: I had suggested that we could show the analysis of the PharMetrics database, not necessarily to speak to outcomes data with irbesartan or Avalide, but to look at the overall safety in the post-marketing arena.

DR. HARRINGTON: If you have that data, yes.

DR. WACLAWSKI: Yes. I would like Dr. Langer, who is responsible for the pharmacovigilance on the project, to make a short presentation of that data.

DR. HARRINGTON: I think that would be terrific.

DR. LANGER: Good morning.

To complement the spontaneous reporting

data, since there are several sources of data that we use for post-marketing surveillance, we did use the PharMetrics database to conduct an epidemiologic study looking at the adverse events of special interest that you have seen previously.

This is a very large managed care claims database which includes approximately 12 million patients from the U.S. general population.

This study actually allowed us to compare initial use of Avalide to irbesartan, because we excluded patients who had any antihypertensive use six months prior to the start of the study.

The study compared the estimated relative risks of the adverse events between Avalide and Avapro users from 1995 to 2006. Now, there are also some other advantages to study this type of database that I would like to mention.

First of all, in the PharMetrics database, you have systematic recording of events coming through medical claims data. We have a well characterized denominator, which is not possible in spontaneous reports. We are also able to control

for certain confounders that we decide on prior to the study, and those can be included in the statistical analysis.

Finally, these data are not subject to certain reporting biases which the spontaneous data do suffer from in regard to the attribution of a possible causal relationship and the likelihood that some decisions about reporting might be influenced by the duration of time that the product is on the market or even the severity of the event.

Now, I should mention that we used approximately 6,000 hypertensive patients on Avalide in this study, and more than 12,000 patients on irbesartan. The patients were treated for an average of one year, but some went on for up to seven years.

Could I have Slide 31-60, please.

[Slide.]

These are the results. They are expressed as a tornado plot. What you see here are point estimates for risk ratios or what we call estimated relative risks with their 95 percent confidence

intervals. You can see that we have included the same events or most of the events that you have seen presented prior in the spontaneous data.

Overall, these point estimates cluster around 1, and the confidence intervals are reasonable, so the analysis we performed confirm what we found in the spontaneous data. There were no safety concerns identified from this analysis.

DR. HARRINGTON: Are these adjusted risk ratios or have you done analyses looking at the comparability of the two groups of patients, because it is not randomized?

DR. LANGER: Right, exactly. In fact, that is one of the things I should have mentioned, that one of the limitations is that they are not randomized, so there may be some residual confounders. But we did adjust for the confounders that we identified prior, and those include--actually, I can show you that information.

Slide 31-79, please.

[Slide.]

Age, gender, history of diabetes,

congestive heart failure, cardiovascular disease, concomitant use of diuretics or other antihypertensives.

DR. TEERLINK: This is actually answering the question I was about to ask. Do you have any further information on the comorbidities of the patients, or is this as much as you have on the baseline characteristics?

DR. LANGER: In this particular analysis, we did not get other information which could be useful, as I think you are implying, such as gallbladder disease, alcohol, substance abuse, obesity, some of the things that might be important in relation to underlying risks.

DR. PAGANINI: On your first slide--

DR. LANGER: The data slide?

DR. PAGANINI: Yes, the data slide with the plot that sort of favored the combination, it excluded diabetics. On the bottom, it seemed to have excluded diabetics, is that correct?

DR. PAGANINI: You want to see the data slide, the tornado plot?

DR. PAGANINI: The tornado plot, please.

DR. LANGER: Yes, 31-60.

[Slide.]

DR. PAGANINI: On the bottom, I can't read it correctly. Does it say diabetics have been excluded?

DR. LANGER: Yes. From the analysis related to nuance of diabetes, we excluded patients with a diagnosis of diabetes prior to entering the study. For the other analysis, we did not, we controlled for that.

DR. PAGANINI: All right. The other question I would have, over this time frame of one year to sometimes seven years, do you have any comparison to hospitalization rates or any comparison to mortality/morbidity statistics with regards to cardiovascular dysfunction or anything like that?

DR. LANGER: In this analysis, we did not look for that.

DR. HARRINGTON: Other questions specific to this and then I will open it up for broader

questions?

Comments, questions? You guys want to go to lunch?

Go ahead Lynn.

Questions from the Committee

DR. WARNER STEVENSON: I would be interested in knowing the basis of data regarding the two medicine and one pill versus two medicine and two pill information.

I haven't looked at this in some time, but the last time I looked at it, it is surprisingly difficult to find information that patients, in fact, are less compliant with two pills unless it means they have to take them at a different time of day.

In fact, the data that I do remember finding suggested that when you move from one to two pills, that sometimes you may actually have better compliance, because now they recognize, okay, this has got to be part of my life and they make a routine for it.

Having said that, I think the data is just

really very thin on compliance related to number of pills. I just wanted to know what your basis of evidence is that it is, in fact, better to combine it than to give them two pills.

DR. WACLAWSKI: Dr. Lapuerta has reviewed that, as well, I would like to have him comment.

Dr. Lapuerta.

DR. LAPUERTA: Putting together a dossier, we looked for these data, and you are right, they are few and far between, but we found three relevant studies. There is a lot of literature on compliance that suggests that fewer pills are better, but we looked for specifically studies that looked at a combination pill versus prescribing of its two individual components separately.

We have found three studies to that regard. Slide 63-53.

[Slide.]

This is a study on the treatment of lipid disorders and hypertension with Caduet, the combination of amlodipine and atorvastatin. It is a retrospective analysis of claims in an elderly

insured population, 2,000 subjects.

Now, this looked at adherence, and adherence was defined as having 80 percent of the days during the study period covered with prescription medication given at the pharmacy.

So, the proportion adherent to the combination here Caduet of amlodipine and atorvastatin was higher than the adherence when the separate components were prescribed.

The two other studies address diabetes in one study and hypertension in the other study.

DR. WARNER STEVENSON: I am sorry. Could we just clarify; so that is an abstract form.

DR. LAPUERTA: Yes, it's an abstract form. Slide 63-54, please.

[Slide.]

This is experience with the metformin-glyburide combination. Again, it is a retrospective analysis from the managed-care population, and we had the same definition of adherence, having 80 percent of days during the study covered by prescription medication given by

the pharmacy.

This looked at patients who were uncontrolled on either metformin or glyburide and then had the second agent added. The second agent could have been added as a separate prescription or added by a single pill, the metformin-glyburide combination. So, those who switched to a combination drug had greater adherence than those who had the second pill prescribed separately.

Slide 63-55, please.

[Slide.]

This is yet another retrospective analysis of managed care data, and this looked specifically at hypertension and persistence with a combination of an ACE and a diuretic. There are fixed-dose combinations available for lisinopril and hydrochlorothiazide, and also enalapril and hydrochlorothiazide.

In each case here, the outcome was persistence, not specifically adherence. Persistence meant that you refilled the medication within 3 times the number of days prescribed. So,

if you had a 1-month prescription, if you refilled your prescription within 3 months, you were considered persistent.

Patients who were prescribed the combination product lisinopril/hydrochlorothiazide were more persistent than patients who received two separate prescriptions, and the same thing for enalapril/HCTZ.

DR. TEMPLE: I should just point out that we have never, as part of our dealing with combinations, insisted that people provide evidence that compliance with the combination is better than the single entities. Companies can't claim that it is, because they have never really shown it except by that stuff, which we are not discussing in great detail.

Conceivably, one could do a trial of this, but you would have to have a low intervention trial. You would have to sort of give the drugs and walk away and see what happens. If you were fastidious and urged people to take them, you probably couldn't find a difference, because

everybody would be on his best behavior, so it is not an easy thing to study in a rigorous way.

I would say that despite those interesting clues, it hasn't been studied rigorously, but I should say we have never insisted on that. If the effects are additive, that has been good enough.

So, all the conclusions that we are talking about here apply equally to using two drugs separately, but starting with two instead of one. It's the same conclusion.

DR. WARNER STEVENSON: In which case I would like to follow up that it would be exceedingly difficult to do an effectiveness analysis of this, simply because it is hard to test it as it is really used.

My experience with combination pills has been at that critical first month that we are talking about is often very poorly adhered to because if you write a combination prescription, in general, about two-thirds of the time it will not be covered.

By the time the patient figures that out

at the pharmacy, gets back to you, you write a letter to the carrier or you write two separate prescriptions now for the two components, in general, that can take up to about a month to actually get a medicine prescribed. I realize that is not your purview, I just think it needs to be said.

DR. TEMPLE: No, no, but you are saying the payers insist on a step care approach, got to fail on one before you get--

DR. WARNER STEVENSON: No, the payers want two separate prescriptions of generic drugs.

DR. TEMPLE: Well, that is different, an interesting matter, right.

DR. WARNER STEVENSON: And I realize it's not our purview, but I think it is the purview of clinicians who have to make these decisions.

DR. HARRINGTON: Other comments?

I would like you to address the second to the last slide you put up where you are starting to talk about the labeling revision. As we get into the questions this afternoon, we will be dealing

with this, and particularly with Dr. Berlowitz here.

I am interested in your thoughts on how do you provide guidance to physicians in this domain. You have shown the relationship between the probability of reaching goal and what your baseline blood pressure is.

What is the research on this that suggests a way that physicians are going to respond? Are we going to respond to these visuals? Are we going to respond to other modalities? Help us understand, so we can give guidance to the FDA as to what might be an effective thing to include n the label.

DR. WACLAWSKI: Perhaps the best answer may come from the clinicians and getting their input with respect to what they would find useful. I am not aware of any data that has systematically looked at the impact of this kind of proposed labeling, because I think we are a little bit on the cutting edge of trying to improve the way the labeling guidance is provided.

DR. HARRINGTON: But I can't believe you

guys haven't done the usual focus groups, et cetera. I mean if we ask the three hypertension experts, we are going to get very nuanced answers. But for Joe or Sally Doc out in the field, who has got the--what did Bill say--7 minutes to see you, what is going to trigger them to behave differently?

DR. WACLAWSKI: A piece of research that we did do was a comparison between a 2-dimensional and a 3-dimensional representation of the blood pressure reductions as a function of blood pressure goal.

Maybe I could walk you through that data because that at least provided some signal as to how physicians find those two alternatives.

DR. HARRINGTON: That would be great.

DR. WACLAWSKI: I won't say it necessarily shows that either one will have a marked impact, but we are looking to try to improve that and try to give physicians better guidance.

So, let me go through that research and its results briefly, and then perhaps Dr. Berlowitz

and Dr. Weber can speak to what they would feel is a reasonable approach to the labeling guidance.

Slide 47-2, please.

[Slide.]

We conducted what you might call focus-group research to determine the utility of a 2-D representation that you saw today in labeling versus a 3-dimensional figure.

A 3-dimensional figure would have the two axes would be baseline blood pressure systolic, baseline blood pressure diastolic, and then the chance of reaching control would be in your Y axis, generating that response surface.

So, we wanted to see how physicians interpret these data, whether they could read off of those curves a blood pressure that would be predicted by the baseline blood pressures, and how they qualitatively sort of assess the usefulness of it.

The methods of that research are on the next Slide 47-3.

[Slide.]

It was an on-line survey with almost 1,000 U.S. physicians that were prescribing or see antihypertensive patients. They were exposed to the product description, general product description, and one of four displays using 2-D representations and 3-D representations of the relationship between control and baseline blood pressure.

They were asked to identify the percent of patients attaining some specific goal blood pressure--that is, read me off of this graph what the chance of reaching a blood pressure goal is, and then get an assessment of how helpful they found these figures in actually coming to that realization. So, let me run through the graphs that were presented.

Graph No. 1 is one of the 3-dimensional graphs on Slide 47-4.

[Slide.]

It shows, in the red, the ARB, the fixed dose combination and the monotherapy underneath it, and on the two axes are the baseline systolic and

baseline diastolic blood pressures with the blood pressure control on the Y axis.

[Slide.]

Graph No. 2, on 47-5, is an example of one of the 2-dimensional plots where we split apart those axes that had the baseline blood pressure systolic and reduced them to 2-D representations. In this case, it was with the combined goal of less than 140/90 on the Y axis.

[Slide.]

Graph No. 3, 47-6, which is what we are proposing for the labeling, actually is very similar to Graph 2 except in this case, the chance of reaching control on systolic blood pressure on the Y axis is specific for the 140 measurement. On the Y axis on the other curve, it is specific through the diastolic of 90.

[Slide.]

Graph No. 4, 47-7, was another representation of a 3-D figure, this time showing for each of those lines on the curve, the percent reaching control that would go on an individual

line as you would do a topographical sort of surface map.

[Slide.]

The results are on 47-8, and what was probably most interesting in the results was some of the responses, you know, the "unable to respond" responses seemed to separate the most. So, in some cases, the 3-D graphs, I think they weren't very well understood by physicians represented by the "unable to respond," whereas, on the 2-D graph, at least we had some responses.

Comprehension, which meant how well were you able to estimate the blood pressure effects or the chance of reaching control ranged, and the ranges are here. They weren't really that different, so once the physician attempted to interpret the graphs, it seems that they were able to do that with similar comprehension, if you will.

The range is there because there were a number of blood pressure values given and a number of responses that generated ranges across them.

Then, again, you see the qualitative

responses are easy to understand and helpful, I think, separating.

So, this was work that we did during our thinking about how to put together the proposed labeling. We had discussions with FDA about how to represent these figures potentially in this, and we conducted this research to take a look at what might be impactful and useful to physicians.

DR. HARRINGTON: I am curious, Bob, as to what you and Norm think, because you are going to have to make the decision as to what this ultimately looks like.

I mean it's almost pitiful what it says about us as a community.

DR. TEMPLE: 3-D really is hard, because it's hard to find where the numbers are on the front to back.

DR. HARRINGTON: I thought maybe it reminded people of taking the SATs or something and they didn't want to.

DR. TEMPLE: Another possibility is that you use both some words and some figures to give

people both a quantitative and a qualitative look to it.

So, maybe it's helpful to say severe because, if you are really in the severe category, you don't have much chance of being controlled. But I am also interested in the other people who won't get to go even though they don't meet the number, because everybody believes they should be lower, and that seems like that should be part of the clinician's judgment how low to go, and he or she should have some idea of how likely that is to happen with a single one or with the combo.

DR. HARRINGTON: That is exactly why I wanted to bring this point up, because both you, or I guess all three of you, you, Mike, and Norm, brought up this morning this notion of is severe the right description, does it tell us enough, how should we provide information for clinicians to make these decisions.

Mike, what do you think? You were the one that started up the notion of the numbers.

DR. LINCOFF: I agree. I mean, I think

the severe provides a severe enough set of values that it is very clear that the success rates are low with monotherapy and that they are higher with the combination. But you almost have the same increment or even better in the lesser degrees that are still within moderate, and I am not sure that we should be arbitrarily deciding it's severe, and not moderate, particularly since the current guidelines combine these into the Stage 2 hypertension, which is a logical subdivision that is reasonable to use.

I think we ought to at least be thinking about if we are going to ultimately decide that it is appropriate to have this as first line, whether severe is overly strict.

Again, I am finding it difficult to be overly conservative here.

DR. TEERLINK: I would echo those sentiments although I think I would also say that we have to limit our discussion a bit to this specific combination.

Inasmuch as I think part of my comfort

would think, gee, maybe we should be extending it beyond to less severe patients is because I am fairly comfortable that the incremental risk in terms of throwing on two agents at one time is seeming to be very low with this combination, whereas, that may not be true for other combinations. So we need to kind of take that into account when we move from the specific case of Avalide to the more generalizable case of combination therapy for hypertension.

DR. HARRINGTON: Yes, and then I think that you will see from the questions that that is going to be a bit of the framework of this afternoon.

We are going to have the specific discussion around this combination, but I think what FDA has asked us to also try to at least think more broadly as to what the requirements might be going forward, and so your comments about the information on the specific agents is going to be something we will talk about this afternoon.

Go ahead, Mike.

DR. LINCOFF: From the more theoretical standpoint, I agree, because what we are left here is trying to make a decision between two therapeutic strategies that seem to have roughly equal risk, but one is clearly more effective than the other, and that is really what it is.

If these were two single separate entities, it wouldn't be nearly that difficult of a decision, I don't think, if we had one entity that had a 20-some percent and the other 40-some percent rate of success with roughly equal safety profiles. Then, I don't think there would be a big discussion about whether or not the more effective one could be first-line therapy.

But because this more effective is a combination of two molecular entities that function at two complementary paths, it is a more complicated decision, and I am not sure why that necessarily has to continue to be the case.

There are some single entities that function at two different paths. I realize the theoretical idea of trying to exhaust the dosing of

a single one before moving on to another but, given the practicalities and the realities of how people actually escalate doses, as well as the fact that some of these side effects are at the higher doses, I wonder why we can't look at these as pretty much just two separate entities comparable.

DR. TEMPLE: It is worth remembering where this started. I mean the drugs that you used to get control of bad people were high-dose diuretics, which as we all know now are potentially lethal and do bad things, hydralazine, considerable side effects, and reserpine.

Well, you might want to think about the heart before you just throw all those in, even though Ser-Ap-Es had its day. But ARBs, it has been very hard to discern dose-related side effects with them, or side effects even at all other than the blood pressure going down too low, and ACE inhibitors except for cough not so different. So, things are different now, I think, for some of the drugs.

DR. HARRINGTON: Right. I think that is

what John Teerlink was getting at.

Other questions or comments?

Did you want Dr. Berlowitz to--

DR. WACLAWSKI: I was going to ask you if you wanted to follow up, because I had gone into the research but hadn't had a chance to have Dr. Berlowitz give some input on labeling guidance and what might help.

DR. BERLOWITZ: Thank you. Certainly there are many issues raised here, and labeling is the one thing that I am probably least able to speak about of anyone in this room. What I feel I do know something about is changing provider practices and certainly how difficult that is.

I think there are a couple of issues here that should be raised. Certainly one way you improve providers' practices is by taking decisions out of their hands, and it is clear I think to myself and to other people here that a combination therapy essentially takes a decision out of their hands in terms of having fewer titrations that are needed.

The other thing that I think is very important is that you need to align the educational messages. Right now there is JNC 7 that is saying one thing and meanwhile you have the tremendous educational efforts through detailing that pharmaceutical companies can provide. That is not able to give that message. They cannot say use a combination.

So, I think efforts at labeling that allows an alignment of the different educational messages would be much more powerful.

DR. HARRINGTON: What about the patient's involvement in all of this? We made reference to the lipid-lowering story earlier this morning, and clearly, many the informed patient comes to see you says, you know, my LDL is such, what are you going to do about it. Most hypertensive patients don't do that to us.

DR. BERLOWITZ: I absolutely agree that patients need to be empowered. They should know what their target threshold is, and, if they are not at there, they should be speaking to their

parent--to their physicians about it. Something else on my mind.

[Laughter.]

DR. TEMPLE: We haven't thought through yet how the change in labeling for all antihypertensives is going to be turned into something that is relevant to patients. We are just trying to figure out the physician part. But we are getting fairly close to writing guidance that will do what the committee advised us to sometime ago, which is to say these things produce strokes, heart attacks, and death. You should know that for antihypertensives.

Surely, that will have an educational component, which is one of the reasons we wanted to do it. We think people don't know enough about getting the pressure down. So, that will be part of all this, too.

DR. WARNER STEVENSON: I would actually just like to ask a point of clarification about the protocol and this information since what we usually do when we see patients is to measure their blood

pressure on their medications.

In both these protocols, in fact, they had their medications withheld on the morning that they were evaluated for the endpoints, so we were seeing the holdover from the previous day. And one might anticipate that being on a volume-reducing agent might have a little more lasting effect.

Could you comment on the blood pressures that you would see in an appointment after having held your medications in that morning compared to what we might usually see in a clinic if we had had our patients take their medications the morning of clinic?

DR. WACLAWSKI: Dr Lapuerta.

DR. LAPUERTA: The original NDA for irbesartan and irbesartan/HCTZ examined the trough peak ratios of the drugs, so to look at when the time of maximum effect was, the peak effect, and what the effect was 24 hours after. So, this study examined trough.

However, with irbesartan and irbesartan/HCTZ, irbesartan/HCTZ in particular, the

difference between peak and trough is not very great. That is one reason why irbesartan is a good once-a-day drug. It seems that the addition of hydrochlorothiazide makes that peak trough even more comparable.

It actually may be fairly similar, perhaps not entirely identical, but fairly similar on irbesartan/HCTZ.

DR. HARRINGTON: Other questions from the committee? I have been told by Cathy here that there is no crime in going to lunch early. It is now 11:35. We will break for an hour, come back at 12:35, and we are going to go right into the questions unless there is other discussion that people would like to have.

Thank you.

[Whereupon, at 11:35 a.m., the proceedings were recessed, to be resumed at 12:35 p.m.]

A F T E R N O O N P R O C E E D I N G S

Questions to the Committee

DR. HARRINGTON: Let's get started.

Many of you picked up outside the questions. We will also show the questions on the screen, on the slides. There is just one of the questions that requires a formal vote. The format we will take is we will have open discussion and ask everyone who would like to, to weigh in on them, and then I will attempt so summarize it and make sure that we have a general feel for what the committee was thinking.

There is what I think is a nice summary preamble to the questions from the Division, that people I think would find helpful. I am going to read just a couple of the sentences, so that people understand the framework with which the questions will be addressed this afternoon.

The first sentence is the Advisory Committee is asked to opine on the basis of granting first-line use to combination antihypertensives and to apply the principles to

Avalide. For the most part, combination antihypertensive products, formulations of two or more drugs for hypertension, have been given an indication for second-line use, similar to what this compound currently has.

As was noted in the presentation this morning, that there are exceptions to recommending single drug initial therapy which are listed. We saw on the slides this morning, as well as in the preamble here. The specific example of losartan/hydrochlorothiazide is discussed, and a statement is made by the Division that it was this latter pathway that was followed for Avalide.

However, in this particular series of trials, irbesartan alone was shown to be effective in achieving goal therapy in 33 percent of the subjects, thus, this population failed to meet the, "very unlikely to reach goal" criteria.

As you heard in Norm's opening remarks this morning, that the Division recognized there were many problems with the current basis for achieving first-line claim and invited the sponsor

to make a case for altering that paradigm, which we heard.

So, the discussion that you will hear this afternoon, I think will take two formats or two pathways, one of which is the specific one dealing with this specific agent, and the second is the broader issue about the approval of combination antihypertensives for first-line use.

You can see on the screen the first question. Again, I will read it.

In considering whether one of these alternatives--meaning the alternative to obtain a first-line claim--is more medically and scientifically sound, in general or in specific cases, the following questions are posed:

1. The vast majority of the studies demonstrating the benefit of antihypertensive drugs in the prevention of cardiovascular events incorporated a stepped therapy approach using single drugs at low doses with titration to the maximum tolerated dose prior to adding a second and third medication.

How does that affect your thinking about the preferred approach to a claim for first-line use for combinations?

That is the first question. Why don't we go around the room to make sure everyone has a chance to be heard. Dr. Ryder, why don't we start with you. We will go around the table.

DR. RYDER: Thank you, Robert. Thank you very much.

I made a comment to Bob Temple at lunch, and I would just like to repeat it for everybody, because I think it is important. From the sponsor's standpoint, I think from a lot of investigators, too--I think this is a great opportunity to discuss the use of combination drugs.

The program with Avalide had a number of very important characteristics. I mean BMS did a great job presenting it. The program was substantial. There are a number of very prespecified endpoints, certain specific populations.

As the committee discusses this, I would ask people to try to dissect out in their own minds, you know, their thinking as to some of the general characteristics that they would be looking for in future programs and also how much they are influenced by the specifics around Avalide itself, which was very, very nicely presented. I think that that is very important.

I have always viewed hypertension--I am sitting in here for John Neylan, so I am really speaking out of turn. My usual committee membership is on endocrine and metabolic, but I do think that this committee is sort of leading the way in many areas of the use of drugs in combination for chronic therapy, and many of the general aspects may even have applicability outside of cardiovascular. That was my comment. Thank you.

DR. HARRINGTON: Steve.

MR. FINDLAY: No comment.

DR. HARRINGTON: Lynn.

DR. WARNER STEVENSON: I think we have

heard quite compelling evidence today that we are not doing an adequate job of controlling hypertension, and I think the issue of beginning with more than one drug certainly makes very good sense.

I think also the theoretical rationale for having less toxicity by combining essentially a partially complete dose of two drugs is also very appealing but must be considered on the virtue of each of those independent drugs alone and separately. We can't really make a lot of generalizations.

So, I think a lot of this is going to be the specifics here of this versus a wider precedent, which I know we are being asked to address. I think that is where we become more uncomfortable.

DR. HARRINGTON: Jason.

DR. HSU: This one I have no comment on.

DR. HARRINGTON: Emil.

DR. PAGANINI: I would comment specifically on the step therapy. I think step

therapy is still probably practiced, but in the clinical world, there are so many different ways of approaching this. One of the steps could be a very broad step of two drugs as your first line.

So, the classic one drug to max, then, the next drug, I think has fallen by the wayside. Most people will start usually, many people will start combinations as their first step towards control.

The second thing that I really think is important is to understand what the individual drugs are. I really mirror what Lynn said. Because two drugs are better than one, or because two drugs are going to eventually end up in a combination, it is very important what those drugs are.

I would not like to see just two drugs thrown together, but rather two drugs that are synergistic, very much so as what we have seen here. So, the idea of having multiple drugs as a first step is probably an acceptable practice. But a very important underlying, say, structure to that first step might be what are those drugs and what

are the individual effects that those drugs have, first, on each other, and, second, on the primary goal of therapy.

DR. HARRINGTON: I will also concur with both Lynn and Emil on the notion that while we are talking about broader issues, we can't forget that there is also a very specific question about this particular combination.

Certainly for me, the framework that was laid out this morning is that, as Bob Temple has noted several times this morning, the drugs have gotten better, that the combination therapy as first-line therapy, may, in fact, be an important thing to think about in part because the drugs have less risk associated with them. They do have less side effects, and so this notion of combining agents becomes a more attractive one.

I was also very struck by one of the last comments that was made by Dr. Berlowitz, with a message that resonated with me. He said, you know, we need to align the messages.

The JNC 7 is saying to think about two

drugs, because two-thirds of patients are going to require them anyway, and yet, without the ability of the industry to talk about that in their educational campaigns with physicians as first-line therapy, we are not doing that. So, the alignment of the messages that Dr. Berlowitz brought up, I thought was an important point.

That is my major comment on this point.

DR. LINCOFF: I sort of interpret this question as asking if because the stepped approach was the therapeutic approach that was shown to reduce cardiovascular events in the treatment of hypertension, can we necessarily extrapolate that to using multiple drugs as the first line. I don't know if that was the intent when it was written, but it sounds like it.

DR. STOCKBRIDGE: It absolutely was.

DR. LINCOFF: I sort of interpret this question as asking if because the stepped approach was the therapeutic approach that was shown to reduce cardiovascular events in the treatment of hypertension, can we necessarily extrapolate that

to using multiple drug as a first line.

I don't know if that was the intent when it was written, but it sounds like it. To that, I think it is very reassuring to see the linkage between reduction in cardiovascular events seems to be associated with a change in blood pressure regardless of how you get there.

I think we have got data from previous presentations and sessions, as well as some of the data that was presented here, that it is less important how you get there in terms of the cardiovascular events and more important how much you reduce the blood pressure and to what targets.

So, with that framework, then, it seems like as long as you have a good tolerability, and this is where the better drugs become important. And, once you have a greater likelihood of achieving that efficacy with the combination approach, we can extrapolate beyond the stepped approach with some degree of confidence.

DR. TEERLINK: I would concur with everything that has been said so far, as well. I

think the general framework that I have been considering as I look at this package, and then think of how to move forward, is as with all of these questions, it is a balancing of the risks and benefits.

On the benefit side, you have the general benefit of lower blood pressure is better, so that addresses this data issue for me to some extent. But then also you have mechanism-specific aspects that Lynn referred to earlier, such as it might matter actually how you get to lower blood pressures. Although lowering blood pressure is good, but you might get additional benefits from lowering blood pressure and inhibiting the renin-angiotensin system.

In addition, on the side of benefits, for combination therapies, there may actually be synergistic effects between certain agents in terms of inhibiting different aspects, different endocrine systems, and getting additional benefit. So, those are the three sides of the benefits that I think need to be addressed.

In terms of the risk side, you have the additional dose-independent risks that come from these combination therapies, which fortunately, in this specific case, are less evident apparently.

But then also you have the dose-dependent risks, and those can either be increased or decreased by the combination therapy. There may be synergisms between the two drugs that could increase actually the dose-dependent risks of the other medication, or the fact that you are able to combine therapies and get the same lower blood pressure for a lower dose may reduce that risk.

So, that is the framework that I am using in general to address this issue. I think in regards to the current available therapy, everything that is available from our data so far suggest that this a beneficial risk/benefit ratio so far.

DR. HARRINGTON: Let me see if I can summarize the thoughts around the table, and then I will ask Drs. Stockbridge and Temple if they have additional questions. I like the way that John

laid it out.

I think he pulled together several people's remarks, first of all, that there is, I think, consensus that, based at this meeting, as well as previous meetings participated in by this panel, that reducing blood pressure in fact is a good thing and can be tied to improvements in cardiovascular outcomes.

That is in a very general way--and we saw some quantitative relationships displayed this morning. And there seems to be a level of comfort in extrapolating those benefits that were gained from the stepped approach to a combination approach. I think several of us have made that comment.

Specifically, though, there is some discussion, and some I will call it caution by the panel, to say that we also need to take into consideration the specific effects of the individual drugs that are being involved, and that would be both on the benefit and risk side, that there may be, as John nicely points out, some

preferential effects of these individual drugs that make up the combination.

There also, as I think Lynn and Emil pointed out, there also may be some adverse effects of the individual components. Finally, the same applies to the combinations. The combinations may be additive, they may be synergistic, they may behave in different ways, and that would all need to be considered, as well.

Have I captured the tone of the first question?

DR. TEMPLE: Yes. Just one thing. We have seen a million combination studies, you know, AB versus A versus B, and it is not easy to conclude anything but that the effects are more or less additive most of the time.

I know when you looked at the black subpopulation, it looked like there might be some synergism there, and there are plausible reasons why that might be true. But, in general, we have not seen synergy.

Since the blood pressure is a little lower